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NEUROBIOLOGICAL RESEARCH ON PTSD

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This issue of the *PTSD Research Quarterly* is devoted entirely to a recently published book, *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to Post-Traumatic Stress Disorder* (Friedman, Charney, & Deutch, 1995). Such an approach represents a departure from our customary format, in which we review a number of articles and chapters that focus on a particular area of PTSD research. We believe, however, that it is completely in the spirit of *Research Quarterly* policy because this book contains 30 chapters that cover most aspects of laboratory and clinical research on neurobiological consequences of stress and trauma.

The guiding principle of this book is that humans exposed to catastrophic stressors utilize the same neurobiological mechanisms that are activated following exposure to a less severe "normal" stressor. Failure to successfully cope with traumatic stress has significant neurobiological consequences. Whereas successful adaptation is followed by a restoration of normal homeostatic balance, unsuccessful adaptation may result in an equilibrium state which, though stable, deviates significantly from normative neurobiological standards. In his chapter, McEwen has called such an abnormal equilibrium "allostasis." The chapter by Yehuda and associates offers evidence suggesting that such an allostatic equilibrium is present in the hypothalamic-pituitary-adrenocortical (HPA) system of patients with PTSD.

The book is divided into five sections that progress from basic neurobiological research on stress, to neurobiological models of stress and PTSD, to specific research on patients with PTSD, to clinical issues regarding diagnosis and treatment, to a final chapter that synthesizes major themes presented throughout the book. Each section is preceded by a brief overview to maintain context and continuity.

Part I, "From Molecules to Behavior: Stress in Laboratory Animals," consists of eight chapters that describe the broad range of techniques and concepts that encompass basic research on stress. Two chapters focus on how stress affects neuronal function. Cullinan and associates describe research on stress-induced immediate-early gene induction while Duman discusses how changes in gene expression affect adaptations of signal induction pathways to both acute and chronic stress. Four chapters review specific neurotransmitter systems involved in stress. The noradrenergic (NE) system is reviewed by Zigmond and colleagues with a specific emphasis on the hippocampus where NE changes may affect memory. Excitatory and inhibitory amino acid systems involved in stress are described by Horger and Roth. Central dopaminergic (DA) systems which are very sensitive to stress are reviewed by Sorg and Kalivas with specific emphasis on how sensitization and cross-sensitization affect DA neurons. Fourth, Stout and associates describe neuropeptides that play a role in the stress response, such as corticotropin releasing factor (CRF), neuropeptide Y, and neurotensin. The chapter by LeDoux moves from studies on specific neurotransmitters to research on the relationship between stress and different forms of learning and memory. The final chapter in this section by McEwen focuses on differences in neuronal adaptation to chronic stress; in some cases these adaptations may be beneficial and in others, detrimental.

Part II, "Models of the Impact of Stress on Brain Function," consists of seven chapters that move beyond identification of which neuronal systems are affected by stress, toward the development of neural models relevant to the impact of stress on humans. Gold and McCarty discuss the mechanisms by which stress affects memory. Deutch and Young present a model of the stress-induced activation of prefrontal cortical DA systems that has implications for subcortical and cortical interactions. Falls and Davis review mechanisms that may mediate fear inhibition, such as extinction and conditioned inhibition. Post and associates review findings suggesting that sensitization and kindling may be important neural substrates of PTSD. Michelson and associates present a model of the effects of stress on the HPA axis that has implications not only for PTSD but also for the effects of stress on human medical disease. Krystal and colleagues review the neurobiology of memory and suggest mechanisms by which PTSD might be associated with memory problems and dissociative phenomena. Finally, Charney and associates synthesize data from a variety of perspectives to develop a functional neuroanatomical model that identifies those brain structures, neurotransmitters, and neural mechanisms that may mediate many of the symptoms associated with PTSD.

Part III, "Adaptive and Maladaptive Responses to Stress in Humans," contains seven chapters on clinical research suggesting that there are similarities

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between the animal and human responses to stress. Prins and associates provide a comprehensive review of abnormalities in sympathetic nervous system responsivity exhibited by PTSD patients. Woodward provides a thoughtful discussion on the complexity of mechanisms underlying the disturbed sleep and dreaming observed in PTSD. Southwick and co-workers focus on neurotransmitter system alterations detected in PTSD patients while Yehuda and colleagues describe the elegant research on HPA axis abnormalities associated with PTSD. Mason and associates focus on profound alterations in thyroid function that appear to be unique to PTSD. The final two chapters in this section focus on important findings in human stress research that have yet to be explored in PTSD. Heninger describes the variety of immunologic deficits that can be detected following exposure to stress, while Williams reviews a number of stress-induced psychological and biological abnormalities that appear to make people especially vulnerable to somatic problems and medical illness.

Part IV, "Clinical Issues," consists of seven chapters that focus on the relevance of animal or human stress/PTSD research on the detection, diagnosis, and treatment of PTSD. Fairbank and colleagues review the epidemiology of PTSD, focusing on prevalence, co-morbidity, and risk factors. Given high rates of co-morbidity among PTSD patients, Friedman and Yehuda present psychobiological assessment strategies that may improve diagnostic precision. Four chapters focus on treatment. Stine and Kosten review the complex neurobiological, diagnostic, and therapeutic issues that must be considered when PTSD is associated with alcoholism or substance abuse. Friedman and Southwick discuss current research on the clinical psychopharmacology of PTSD from a neurobiological perspective. Foa and associates review cognitive behavioral therapy of PTSD while Marmar and colleagues provide a comprehensive review of dynamic psychotherapy for PTSD. Finally, Friedman and Schnurr show that the preponderance of evidence indicates that traumatized individuals, especially those who develop PTSD, appear to be at increased risk for medical illness.

Part V, "Summary," written by the editors, presents a series of questions that synthesize some of the major themes presented throughout the book. They close with a six-point agenda for future research on PTSD that emphasizes: more investigations on basic neurobiological and psychological mechanisms, greater emphasis on theory-driven research, intensification of efforts to understand the pathophysiology of PTSD, application of laboratory paradigms to psychobiological diagnostic protocols, more randomized psychopharmacological clinical trials, and attention to the impact of traumatic stress and PTSD on physical health.

The editors hope that this book will motivate: basic biobehavioral scientists to test laboratory paradigms that are informed by clinical observations and questions; clinical researchers to investigate questions about PTSD from the broader perspective of coping and adaptation; and clinicians to conceptualize diagnostic and therapeutic questions from a neurobiological theoretical perspective.

Friedman, M.J., Charney, D.S., & Deutch, A.Y. (Eds.). (1995). *Neurobiological and clinical consequences of stress: From normal adaptation to PTSD*. Philadelphia: Lippincott-Raven.

CHAPTER ABSTRACTS
Adapted from Text

Part I. From Molecules to Behavior: Stress in Laboratory Animals

CULLINAN, W.E., HERMAN, J.P., HELMREICH, D.L., & WATSON, S.J. **A neuroanatomy of stress.** (pp. 3-26). We will briefly summarize some of what is known regarding the organization of neural circuitry underlying integration of the stress response, focusing initially on putative activational pathways, followed by a review of possible negative feedback mechanisms. We will also review recent evidence from functional/anatomical studies aimed at disclosing neural pathways mediating responses to acute stressors. While significant progress has been made in delineating pathways by which modality-specific inputs access the hypothalamic-pituitary-adrenocortical (HPA) axis, relatively little is understood about possible points of integration proximal to the hypophysiotropic paraventricular nucleus neuron. Also requiring clarification is the nature of the glucocorticoid feedback signal in the context of the acute response to stress. Furthermore, the neuronal pathways mediating negative feedback remain to be firmly established. Future attempts at elucidating these issues may be aided by activity-based immediate-early gene mapping, which appears to represent a powerful new approach to delineating circuit components responsible for orchestrating HPA responses.

DUMAN, R.S. **Regulation of intracellular signal transduction and gene expression by stress.** (pp. 27-43). The actions of stress on many neurotransmitter and neuropeptide systems result in regulation of receptor-coupled intracellular signal transduction pathways. These signal transduction pathways mediate many of the short- and long-term effects of stress on neuronal function. Continued exposure to stressful stimuli may lead to additional modulatory changes, some of which may be beneficial. However, other chronic effects of stress may be maladaptive and may thereby underlie, or contribute to, stress-related psychiatric disorders such as PTSD and depression. The present chapter provides an overview of the intracellular pathways that mediate the actions of acute stress. In addition, examples of adaptations of signal transduction pathways and gene expression to chronic stress are discussed. Many of the acute and chronic actions of stress most likely evolved as "positive" adaptive responses that should increase the survival and behavioral performance of the animal in response to subsequent environmental stressors. Other actions of chronic stress could represent "negative" adaptations that have adverse side effects on neuronal function and behavior.

ZIGMOND, M.J., FINLAY, J.M., & SVED, A.F. **Neurochemical studies of central noradrenergic responses to acute and chronic stress: Implications for normal and abnormal behavior.** (pp. 45-60). We will begin by summarizing the basic characteristics of noradrenergic neurons in brain. Several features of noradrenergic neurons are consistent with their putative role as elements within a diffuse, modulatory system participating in the response to stress. Then we will discuss their response to acute and chronic

stress. Finally, we will comment on the functional implications of these findings. Stimulation of locus coeruleus neurons produces the appearance of behaviors normally associated with stress, whereas lesions seem to reduce such behaviors. If the relation between arousal and performance is represented by an inverted U-shaped curve, can the sensitization of norepinephrine release that occurs with chronic stress represent too much of a good thing? Several investigators have recently called attention to this possibility, further suggesting that PTSD may be one manifestation of a hyperactive central noradrenergic system.

HORGER, B.A. & ROTH, R.H. **Stress and central amino acid systems.** (pp. 61-81). There are a number of amino acids in the mammalian central nervous system (CNS) believed to have a role in synaptic transmission. Amino acids have been separated into two general classes, excitatory amino acids (EAA) (glutamate, aspartate, homocysteic acid, and cysteic acid) that depolarize neurons in the mammalian CNS and inhibitory amino acids (γ-aminobutyric acid (GABA), glycine, taurine, and β-alanine) that hyperpolarize mammalian CNS neurons. Amino acid transmitters have been shown to have a role in the organism's response to physical (i.e., pain or discomfort) or psychological (i.e., fear) stress. Stress-inducing procedures reduce the number of GABA binding sites and increase benzodiazepine binding sites in the cortex. Exposure to stress also produces an increase in extracellular levels of EAA transmitters in the cortex and other regions. This chapter is a review of the responses of central amino acid systems to stress and the neurobiological consequences of these responses.

SORG, B.A. & KALIVAS, P.W. **Stress and neuronal sensitization.** (pp. 83-102). In humans, stress-precipitated psychoses such as panic disorder and PTSD resemble behavioral sensitization in rodents. Studies in animal models indicate that recruitment of hormonal systems involved in the stress response may importantly facilitate several behaviors, including sensitization to stress and psychostimulants. The physiological substrates involved in stress- and psychostimulant-induced changes in behavior lie in the brain dopaminergic pathways. Evidence to date shows that the neural substrates critical for development and expression of behavioral sensitization to psychostimulants include the ventral tegmental area and nucleus accumbens, respectively. Norepinephrine and serotonin are also altered by stress and psychostimulants, and interactions between corticotropin-releasing hormone (CRH) and corticosterone (CORT) with these neurotransmitter systems has been demonstrated. The role of CRH and CORT in the initiation and/or expression of behavioral sensitization remains unclear.

STOUT, S.C., KILTS, C.D., & NUMERO, C.B. **Neuropeptides and stress: Preclinical findings and implications for pathophysiology.** (pp. 103-123). In this chapter we discuss salient evidence concerning those neuropeptides that appear to play a role in the stress response. Where possible, we will delineate the particular stressor that has been reported to alter peptidergic neurotransmission. Our discussion begins with corticotropin-releasing factor (CRF), for which the most overwhelming evidence exists for a widespread role in the stress response. Next we consider the neurohypophysial peptides that interact with CRF in certain functions. The remaining peptides are then discussed, from those with well-established roles in mediating stress responses to a few neuropeptides for which the evidence is slight. Finally, we consider briefly the application of preclinical data to the study of neuropeptide involvement in clinical states such as PTSD. Note that unless otherwise specified, all data come from studies in rats.

LEDOUX, J.E. **Setting "stress" into motion: Brain mechanisms of stimulus evaluation.** (pp. 125-134). In this chapter I will describe research that has identified neural systems that underlie the evaluation of the emotional significance of environmental stimuli, especially research that has used the techniques of classical fear conditioning to study emotional mechanisms. I will focus on research using the elicitation of species-typical defensive behavior (freezing) and increases in arterial pressure as conditioned responses by a tone conditioned stimulus (CS) paired with a shock unconditioned stimulus. The amygdala is involved in fear conditioning independent of the sensory modality of the CS and the motor modality of the unconditioned response. The amygdala is likely to be a site where sensory information is transformed into emotional control signals, allowing the determination of whether environmental threats exist and, if so, determining what they are and how they should be responded to. A good deal of evidence suggests that the amygdala is also involved in processing positive valence stimuli, signals for reward.

MCEWEN, B.S. **Adrenal steroid actions on brain: Dissecting the fine line between protection and damage.** (pp. 135-147). Adrenal steroids play a vital role in containing the body and brain response to stressful events; as long as adrenal secretion is itself contained, adaptation occurs. However, when adrenocortical secretion is no longer self-regulated and becomes persistently elevated, there are several negative consequences, including: 1) neuronal atrophy in hippocampus and associated cognitive impairment; 2) imbalances within the 5-HT system due to elevated 5-HT_2 and suppressed 5-HT_{1A} receptors, which may enhance anxiety and reduce the ability to suppress memories of aversive associations; and 3) elevated insulin and corticosteroids, which increase fat deposition and can increase atherosclerosis. These consequences may reduce effective cognitive processing of and coping with threatening events. This review will summarize these effects and comment on their relevance to the pathophysiology of two stress-related disorders: PTSD and endogenous depressive illness.

Part II. Models of the Impact of Stress on Brain Function

GOLD, P.E. & MCCARTY, R.C. **Stress regulation of memory processes: Role of peripheral catecholamines and glucose.** (pp. 151-162). The findings reviewed in this chapter document some of the evidence indicating that stress-related neurobiological responses to an experience can regulate the formation of memory for that experience. Moderate stress levels enhance memory while high stress levels impair memory. This view is most clearly defined for epinephrine, but applies also to glucose and to many drugs directed at different neurotransmitter systems. The findings described here also point to control of circulating glucose levels, with subsequent actions on the central nervous system, as an important intermediate step between sympathetic-adrenal medullary functions and actions on cognitive functions. An interesting and less well studied component of this field of study is the degree to which sympathetic-adrenal medullary responses are themselves based on an organism's past experience. It is easy to imagine that habituation and sensitization of sympathetic responses based on earlier experiences would result in individuals who might respond to similar new experiences with either diminished or exaggerated sympathetic activity.

DEUTCH, A.Y. & YOUNG, C.D. **A model of the stress-induced activation of prefrontal cortical dopamine systems: Coping and the development of post-traumatic stress disorder.** (pp. 163-175). In many ways, the cortical dopamine (DA) response to

stress can be considered a microcosm of the central changes thought to occur in PTSD. We will briefly review regulation of the DA neurons that innervate the prefrontal cortex (PFC), present a model for the genesis of the stress-induced increase in PFC DA release, and attempt to relate the function of dopaminergic regulation of PFC neurons to a more widespread network of sites (including the amygdala) that are functionally coupled in stress. We will discuss the PFC in relation to a more widespread stress "system" that involves the amygdala. We will also try to minimize the redundancy with other contributions to this volume, and refer readers to these other chapters for more detailed descriptions of certain aspects of the stress response.

FALLS, W.A. & DAVIS, M. **Behavioral and physiological analysis of fear inhibition: Extinction and conditioned inhibition.** (pp. 177-202). This chapter will review selected aspects of the literature on two phenomena, extinction and conditioned inhibition, which deal with fear reduction and have considerable relevance to the problems seen in psychiatric disorders such as post-traumatic stress syndrome. It will begin by reviewing the theories of extinction put forth by Pavlov and later by Konorski as these have been influential in modern thinking about extinction. It will then discuss at some length whether extinction results from an erasure of the original memory or a buildup of competing inhibition, a critical distinction for an eventual analysis of brain systems involved in extinction. The relationship between extinction and conditioned inhibition and the paradox of avoidance behavior relevant to extinction will be covered next. Clinical implications of data related to extinction and avoidance behavior will then be reviewed. Finally, brain structures and neurotransmitters involved in extinction will be discussed. The review will be restricted to Pavlovian fear conditioning and avoidance conditioning.

POST, R.M., WEISS, S.R.B., & SMITH, M.A. **Sensitization and kindling: Implications for the evolving neural substrates of post-traumatic stress disorder.** (pp. 203-224). Behavioral sensitization and kindling have in common the ability to increase behavioral or physiological responsivity to repeated presentation of the same inducing stimulus. We suggest that some of the principles involved in laying down the differential memory traces of sensitization and kindling may be useful bridging structures for considering parallel processes in different neural substrates that could be occurring in the related processes of stress sensitization and memory "branding" in PTSD. We suggest that these models may provide a primitive template for considering how acute or repeated stressors may not only leave permanent memory traces, but also affect the biochemistry and microstructure of the brain, potentially by impacting immediate-early-gene- and late-effector-gene expression. Stress sensitization and kindling also have their own spatiotemporal unfolding of cascades of neurobiological events that may have important mechanistic and pharmacotherapeutic implications.

MICHELSON, D., LICINIO, J., & GOLD, P.W. **Mediation of the stress response by the hypothalamic-pituitary-adrenal axis.** (pp. 225-238). The hypothalamic-pituitary-adrenal (HPA) axis is a complex system whose components work together under both nonstressed and stressed conditions. At low levels of activity it acts with a circadian rhythm and is a "permissive" system. Under stressful conditions the system is activated and works to maximize the body's ability to respond effectively to disturbances in homeostasis as well as to counterregulate many of the potentially harmful effects of activation of other stress-activated responses. We will review the physiology and regulation of the HPA axis, describe how it affects the organism as a whole during the stress response, and consider how alterations in HPA axis function might contribute to the pathophysiology of various disease states. The effects of development on the organization of the HPA axis, the effects of manipulations of the internal glucocorticoid milieu, and the effects of environmental manipulations on the reactivity of the axis to stress may be relevant to the body of data documenting the importance of early life experience in disorders of stress response such as depression. At the same time, animal models such as the LEW/N and F344/N rats, which exhibit genetically based differences in HPA axis activation in response to stressors, suggest that HPA axis excitability is also governed by inheritance.

KRYSTAL, J.H., BENNETT, A.L., BREMNER, J.D., SOUTHWICK, S.M., & CHARNEY, D.S. **Toward a cognitive neuroscience of dissociation and altered memory functions in post-traumatic stress disorder.** (pp. 239-269). The purpose of this review is to highlight recent progress made in studies of the neurobiology of dissociative states, memory dysfunction, and hyperarousal in PTSD patients. This chapter will review and begin to integrate recent studies of PTSD patients, other patient populations, healthy subjects, and preclinical research. In reviewing this diverse body of literature, we will highlight the potential prognostic and therapeutic significance of recent research findings as a stimulus for future research on the neurobiology of dissociative states and memory disturbance in PTSD. This chapter's cognitive neuroscience perspective assumed that the features of traumatic memories and dissociative states in PTSD are properties of the underlying neural networks mediating these functions.

CHARNEY, D.S., DEUTCH, A.Y., SOUTHWICK, S.M., & KRYSTAL, J.H. **Neural circuits and mechanisms of post-traumatic stress disorder.** (pp. 271-287). Preclinical and clinical investigations provide strong evidence for linking several brain structures to the signs and symptoms of anxiety and fear associated with trauma. Chief among these are the amygdala, locus coeruleus, hippocampus, hypothalamus, thalamus, periaqueductal gray, and orbitofrontal cortex. The neuroanatomy, neurochemistry, and neural mechanisms relevant to the role these brain structures play in anxiety and fear are reviewed. The neural circuit and neural mechanisms of anxiety and fear described in this chapter may have implications for the psychotherapy and pharmacotherapy of PTSD. The concepts discussed in this chapter also suggest potentially fruitful approaches toward development of new therapeutic drugs for PTSD.

Part III. Adaptive and Maladaptive Responses to Stress in Humans

PRINS, A., KALOUPEK, D.G., & KEANE, T.M. **Psychophysiological evidence for autonomic arousal and startle in traumatized adult populations.** (pp. 291-314). In this chapter, we will first review laboratory studies that have presented representations of traumatic events to adults with and without PTSD. Neither biological challenge studies nor studies that have examined the psychophysiological impact of talking about a trauma will be covered. However, we will examine potential differences in baseline levels of arousal and psychophysiological responding to other types of laboratory stressors. Physiological activity will be characterized as autonomic activity even though the effects in question might be due to sympathetic activation, parasympathetic withdrawal, or both. Our review will focus on heart rate and skin conductance because they are the most widely used

measures of general autonomic nervous system activity and appear to be the best discriminators between individuals with and without the PTSD diagnosis. Finally, we will consider the literature on exaggerated startle responses in adults with and without PTSD. Following this review, we will address the need to consider individual differences in reactivity, as well as situational and methodological variables influencing psychophysiological responding in future research on the psychophysiology of PTSD.

WOODWARD, S.H. **Neurobiological perspectives on sleep in post-traumatic stress disorder.** (pp. 315-333). We have reviewed aspects of sleep neurobiology potentially relevant to an understanding of sleep disturbance in PTSD. We have focused on possible overlaps between noradrenergic and cholinergic mechanisms implicated in both sleep and response to stress. We next examined the intimate anatomic and functional interaction between cholinergic brainstem nuclei subserving both startle-related defense behavior and rapid-eye-movement (REM) sleep. An alternative model of locus coeruleus-noradrenaline based non-REM stage 1 nightmares compatible with continuous state theory of dreaming was proposed. We next considered the topic of REM pressure, seemingly overdetermined by putative brainstem and receptor adaptations associated with PTSD, yet inconsistently observed in PTSD patients. A number of obstacles to the exploration of sleep continuity disturbance in PTSD were noted, mostly deriving from reliance upon traditional laboratory polysomnography. A plea was also entered for the application of "challenge" studies using both auditory and pharmacological probes.

SOUTHWICK, S.M., YEHUDA, R., & MORGAN, C.A. **Clinical studies of neurotransmitter alterations in post-traumatic stress disorder.** (pp. 335-349). In this chapter we describe and summarize clinical studies of neurotransmitter alterations in PTSD. We focus primarily on sympathetic nervous system neurotransmitters (norepinephrine, epinephrine, and dopamine), although mention will be made of opiate and serotonin systems. Baseline or resting studies generally have found no differences in plasma catecholamine levels between combat veterans with PTSD and normal controls. In contrast, most 24-hour urine studies have reported increased excretion of catecholamines and most challenge studies have found evidence for hyperresponsivity of catecholaminergic systems. Investigations point to an increased responsivity of the sympathetic nervous system detectable under conditions of "stress" in severely traumatized individuals with PTSD. Findings are consistent with a behavioral sensitization model of PTSD.

YEHUDA, R., GILLER, E.L., LEVENGOOD, R.A., SOUTHWICK, S.M., & SIEVER, L.J. **Hypothalamic-pituitary-adrenal functioning in post-traumatic stress disorder: Expanding the concept of the stress response spectrum.** (pp. 351-365). This chapter will review the literature on hypothalamic-pituitary-adrenal (HPA) axis functioning in PTSD. The conclusion that will emerge from a review of these findings is that the alterations that have been noted in PTSD differ dramatically from those that have been described in most studies of the normative stress response. Furthermore, the HPA axis findings in PTSD are distinct from those reported in other psychiatric conditions, even conditions with similar symptoms to PTSD, such as major depressive disorder. A model of HPA axis functioning that has been put forth to explain these alterations will be described. The distinctness of the HPA axis findings in PTSD raises two basic conceptual issues that will also be the focus of discussion. The first issue bears on the formulation of PTSD as a normative consequence of stress. The second issue raised concerns the narrowness of current formulations of the normative stress response.

MASON, J.W., WANG, S., YEHUDA, R., BREMNER, J.D., RINEY, S.J., LUBIN, H., JOHNSON, D.R., SOUTHWICK, S.M., & CHARNEY, D.S. **Some approaches to the study of the clinical implications of thyroid alterations in post-traumatic stress disorder.** (pp. 367-379). We have recently reported that many PTSD patients show persistent and disproportionate elevations in both total and free triiodothyronine (T3) in relation to free thyroxine (T4); this elevates the T3/T4 ratio, suggesting that there may be increased peripheral conversion of T4 and T3 in this disorder. The nature of the observed changes in PTSD are not those of classical or other established forms of clinical hyperthyroidism, but rather of a more subtle, unusual, and perhaps even distinctive type of moderate hyperactivity featuring total and free T3 elevations that are not detected by conventional routine clinical thyroid screening tests. It appears very important to compare the thyroid profile in PTSD patients under highly protective, sanctuary-like conditions—in contrast to heavy-demand, group-oriented conditions—cross-sectionally but especially longitudinally. Another important issue in our experience relates to methodological questions concerning the administration and interpretation of psychometric tests in PTSD studies.

HENINGER, G.R. **Neuroimmunology of stress.** (pp. 381-401). This chapter will review: 1) the current state of knowledge about the mechanisms that subserve central nervous system (CNS)-immune-system interactions during stress; 2) the evidence that psychologic and behavioral stress can alter and impair immune function; and 3) recent data on the mechanisms by which immune function and activation may influence CNS activity. There are several ways that the CNS stress response can modify immune function, including activation of the hypothalamic pituitary adrenal (HPA) axis, and of the sympathetic nervous system adrenergic and opiate systems. One negative feedback loop that has been identified involves immune activation releasing interleukin-1 into plasma, which in turn stimulates corticotropin-releasing factor release with a consequent increase in adrenal steroids, which in turn inhibits immune activation. Overall, the data suggest that many of the adverse health consequences of stress may be mediated through the immune system.

WILLIAMS, R.B. **Somatic consequences of stress.** (pp. 403-412). There are psychological characteristics (hostile personality trait, depressed state) and environmental characteristics (high demand/low control, low social support) that have been shown to have somatic consequences severe enough to have significant adverse impact on disease and death. These characteristics are associated with biobehavioral characteristics that are biologically plausible mediators of the adverse health effects. Further research has the potential to identify both peripheral molecular and central nervous system (CNS) neurobiological substrates (e.g., reduced CNS serotonergic function) that mediate the health-damaging effects of these psychological and environmental characteristics. Ultimately, our knowledge of these health-damaging characteristics, their pathogenic mechanisms, and their neurobiological substrates should lead to more effective means of prevention and treatment.

Part IV. Clinical Issues

FAIRBANK, J.A., SCHLENGER, W.E., SAIGH, P.A., & DAVIDSON, J.R.T. **An epidemiologic profile of post-traumatic**

stress disorder: Prevalence, comorbidity, and risk factors. (pp. 415-427). The studies discussed in this chapter suggest that PTSD is an important and continuing public health problem, especially among at-risk groups such as survivors of war and criminal activity. Epidemiologic studies have demonstrated that although many kinds of extreme events can cause PTSD (e.g., exposure to combat, criminal victimization, natural disasters), not all of those exposed will develop the disorder. Evidence suggests that exposure to extreme events may be more common than once thought, and that risk factors include characteristics of the person at the time of exposure to the extreme event, characteristics of the event itself, and characteristics of the post-exposure environment. Studies are needed that focus on determining the direct and indirect contributions of trauma exposure to rates of PTSD in specific populations through the psychological, social/environmental, and neurobiologic mechanisms comprehensively discussed in the other chapters of this book.

FRIEDMAN, M.J. & YEHUDA, R. **Post-traumatic stress disorder and comorbidity: Psychobiological approaches to differential diagnosis.** (pp. 429-445). The purpose of this chapter is to consider whether, and to what extent, issues of diagnostic comorbidity or differential diagnosis can be better understood—conceptually and practically—in the context of psychobiological findings of PTSD. Our strategy will be to review the evidence for psychiatric comorbidity and explore the phenomenologic similarities and differences between PTSD and three other disorders—major depressive disorder, panic disorder and generalized anxiety disorder—that are often associated with PTSD. We will present and clarify the issues that must be addressed by clinicians performing a diagnostic assessment for PTSD and other possible comorbid diagnoses. Next, we will discuss the potential utility of biological findings to clarify some of these issues, and review laboratory-based abnormalities associated with PTSD for the purpose of identifying those procedures that may be most useful and clinically applicable in distinguishing PTSD from other disorders. Finally, we will discuss new research findings that may offer new diagnostic approaches.

STINE, S.M. & KOSTEN, T.R. **Complications of chemical abuse and dependency.** (pp. 447-464). This chapter will focus on the complexities of the interaction between comorbid PTSD and substance abuse conditions, and the implications that this interaction has for clinical treatment. Pharmacological treatment issues that reflect the interaction of these disorders will be considered. No one-to-one correspondence can be expected between a PTSD and substance abuse diagnosis and any one method of psychological or pharmacological treatment. Some initial progress has been made in treatment matching to identify patient subgroups best treated with specific approaches. The concept of self-medication, if used judiciously, can be useful in understanding the relationships between substance abuse and PTSD symptoms, the biological systems affected, and the drugs patients choose to abuse, and can generate useful hypotheses in the design of needed studies.

FRIEDMAN, M.J. & SOUTHWICK, S.M. **Towards pharmacotherapy for post-traumatic stress disorder.** (pp. 465-481). We review the current literature on the clinical psychopharmacology of PTSD. We have failed to discover a pharmacological silver bullet, a single drug that will significantly reduce PTSD symptoms. Certain drugs may be helpful in alleviating specific PTSD symptom clusters. Reexperiencing symptoms appear to respond to tricyclic antidepressants and monoamine oxidase inhibitors, avoidant/numbing symptoms may respond to selective serotonin reuptake inhibitors (and possibly to valproate), and arousal symptoms seem to respond to antiadrenergic agents. A rational approach to pharmacotherapy for PTSD may require a multisystem approach in which multiple drugs, each one with a unique and distinct action, are administered simultaneously.

FOA, E., ROTHBAUM, B.O., & MOLNAR, C. **Cognitive-behavioral therapy of post-traumatic stress disorder.** (pp. 483-494). This chapter offers a review of studies examining cognitive-behavioral interventions. There is a special focus on those employed with female assault survivors. Only group studies or case reports that included at least semistructured procedures for evaluating treatment outcome were included. We begin our review with a general description of cognitive-behavioral procedures. We then examine literature regarding the efficacy of these procedures with post-traumatic stress symptoms. Finally, we propose mechanisms to explain the success that cognitive behavioral procedures have had in alleviating post-traumatic stress symptoms. Overall, results from well-controlled studies and case reports converge. Results indicate that both exposure and anxiety management training programs are effective in reducing PTSD symptoms and related psychopathology such as depression.

MARMAR, C.R., WEISS, D.S., & PYNOOS, R.S. **Dynamic psychotherapy of post-traumatic stress disorder.** (pp. 495-506). Psychodynamic approaches to the understanding of traumatic stress emphasize the impact of a traumatic event on the person's self concepts and view of others, affects resulting when: 1) conscious and unconscious representations of the self and others triggered by the trauma are discrepant with usual views, and 2) defenses are mobilized to cope with the discrepant meanings and painful emotions. Successful psychodynamic treatment, especially when provided early in the course of the development of PTSD, may ameliorate the development of chronic stable biologic changes resulting from traumatic stress exposure. For uncomplicated post-traumatic stress disorders, brief dynamic psychotherapy, or time-limited cognitive-behavioral treatments emphasizing exposure strategies and cognitive restructuring, are effective treatments. When PTSD is comorbid with panic disorder, partial agoraphobia, major depressive episode, and related disorders, the addition of specific psychotherapeutic and pharmacotherapeutic treatments for these conditions is indicated. For post-traumatic personality disorder in trauma victims with decades of unresolved traumatic stress symptomatology, extensive secondary adversities, and complex comorbidities, long-term multimodal integrated treatment offers the greatest hope.

FRIEDMAN, M.J. & SCHNURR, P.P. **The relationship between trauma, post-traumatic stress disorder, and physical health.** (pp. 507-524). First we review the literature on the physical health outcomes associated with traumatic events. Despite the extensive literature suggesting that exposure to stressful events may be associated with adverse health outcomes, much less has been written on the medical and somatic consequences of exposure to extreme stress. Nonetheless, reviewers have suggested that physical health may be severely and chronically impaired following traumatic experiences. Second, we review the literature on the physical health outcomes associated with PTSD. We argue that PTSD is an important mediator through which trauma may be related to adverse outcomes. Third, we review biological and psychological correlates of PTSD that might predispose affected individuals toward increased risk for medical problems.

Part V. Summary

FRIEDMAN, M.J., CHARNEY, D.S., & DEUTCH, A.Y. **Key questions and a research agenda for the future.** (pp. 527-533). To our knowledge, this book represents the first comprehensive effort to conceptualize PTSD in terms of the basic neurobiological mechanisms that promote normal adaptation to stress. In our own effort to synthesize some of the major themes presented throughout this book, we offer the following questions: What defines "normal" as opposed to "traumatic" stress?; What differentiates normal from traumatic stress?; What are the major similarities and differences between the neurobiology of the stress response generally observed experimentally, and that observed among PTSD patients?; What neurobiological aspects of the stress response have yet to be explored in PTSD?; To what degree do peripheral events influence central neuronal function in PTSD?; Do the somatic consequences of stress help us understand the adverse health findings associated with exposure to traumatic events and PTSD?; Which neural mechanisms seem most applicable to PTSD? Which neural mechanisms of memory seem most applicable to PTSD?; Is allostasis a useful concept for PTSD?; What animal models are applicable to PTSD?; Are there any useful clinical applications of laboratory paradigms currently used in PTSD research with humans?; Where should we direct future research on the clinical pharmacology of PTSD?; How can we understand, from a neurobiological perspective, the fact that PTSD is usually associated with at least one other comorbid psychiatric disorder?; and What should be the future agenda for research on PTSD?

PILOTS UPDATE

There is a new way to connect to the PILOTS database—and to a great many other resources for the traumatic stress researcher or clinician. The National Center for PTSD has opened its own Home Page on the World Wide Web.

What is the World Wide Web? It is a way of navigating through cyberspace, a system of links among computers across the world that greatly simplifies the process of finding and using the millions of files that individuals, organizations, corporations, and governments put up on computers for public access and use. Instead of typing in a separate command for each file you wish to access and each interaction you wish to have with it; instead of working your way through menu after menu of choices; all you do is point your mouse and click, just as if you were using files on your own hard disk. And for those without Macintosh, Windows, or another graphic user interface, there are ways of using the World Wide Web that require nothing more than an ordinary computer keyboard.

To use the World Wide Web, you need a computer (or a terminal) with a link to the Internet. You also need a piece of software called a "web browser." Popular browser programs include Mosaic and Netscape; Lynx is widely used among those without graphical interfaces. To link to a web site, you simply type in its address (called a uniform resource locator, or URL), and the browser opens a connection to it. Many browsers can keep a list of URLs, so that once you have typed one in you need never do so again. And most browsers can perform a variety of tasks, such as retrieving and downloading files from another computer (replacing the "ftp" command), interacting with a file on another machine ("telnet"), and sending electronic mail.

From the information provider's point of view, the advantage of the World Wide Web is that it allows the gathering in one location of pointers to a wide range of related information resources, which may in fact reside on computers scattered around the world. There may be several web sites dealing with the same subject, each from a different organizational perspective. But this does not mean that the resources themselves are unnecessarily duplicated. For example, there may be half a dozen web sites offering access to the PILOTS database: but they all point to the same place, the PILOTS file on the Dartmouth College Library Online System.

The World Wide Web address (URL) for our new Home Page is:

`http://www.dartmouth.edu/dms/ptsd/`

Like many web sites, its contents will be constantly changing as new resources are added, existing ones updated, and links to other sites expanded. Right now it offers the following:

- Information about the National Center for PTSD and its seven divisions
- A link to the PILOTS database
- Brief instructions for searching PILOTS
- Downloading of the *PILOTS Database User's Guide* and the *PILOTS Database Instruments Authority List*
- Downloading of back issues of the *PTSD Research Quarterly*
- Links to other World Wide Web sites dealing with PTSD

Future additions will include:

- Staff directory of all National Center divisions, with direct email links to divisions and their staff members
- Back issues of the *NCP Clinical Quarterly*
- National Center annual reports
- Order forms for National Center publications sold by the Superintendent of Documents, the National Technical Information Service, and other government publishers
- Listing of positions available in the National Center for PTSD
- Selected papers by National Center staff members
- Bibliographies on special topics
- Directory of PTSD programs within the Department of Veterans Affairs
- Basic information on PTSD for veterans, their families, and members of the public
- Recommended reading lists for students, patients, and others

These will be added over the course of the next year. We hope to work closely with staff members from all seven divisions of the National Center, to ensure that our Home Page will provide convenient, user-friendly access to the widest possible range of authoritative information resources. We welcome all comments and suggestions from users and potential users.

IMPORTANT NOTICE TO OUR VA SUBSCRIBERS:
KEEP YOUR *RESEARCH QUARTERLY* COMING

If you are receiving a copy of the *PTSD Research Quarterly* personally addressed to you at your VA address, and the code 99 appears on the mailing label on your copy of this issue, you need to let us know that your address is correct and that you wish to continue receiving the *Research Quarterly*. To do this, just photocopy this page, which includes your mailing label, and return it to us (at the return address shown below). If you need to correct your VA address, please type or print the new address next to the old one.

JOURNAL OF TRAUMATIC STRESS NOMINATIONS FOR EDITOR SOUGHT

Nominations are sought by the Scientific Publications Committee of the International Society for Traumatic Stress Studies (ISTSS) for the position of Editor of the *Journal of Traumatic Stress*. The individual selected as Editor will assume responsibilities as Editor-elect on January 1, 1997. The term of office will be for 5 years, preceded by a year as Editor-elect.

Successful candidates will have experience and expertise in traumatic stress research, theoretical conceptualizations of the field, and treatment outcome. S/he will possess a reputation for scholarship and be sensitive and open to activity in the field broadly defined. Prior experience as an editor/reviewer for journals and funding agencies is essential. Institutional support from a candidate's employer is very important.

Applicants must be members in good standing of ISTSS. Members are encouraged to nominate qualified candidates as well as to self-nominate. Nominations from minority candidates are particularly welcome. Interested individuals should forward a curriculum vitae and a letter detailing qualifications to Terence M. Keane, Ph.D., Chair, Scientific Publications Committee, ISTSS, 60 Revere Drive, Suite 500, Northbrook, Illinois, USA, 60062. Deadline for submissions is March 1, 1996.

JTS SPECIAL ISSUE ON TRAUMATIC MEMORY

The October 1995 issue of the *Journal of Traumatic Stress* (Volume 8, Issue 4) is devoted to traumatic memory research. It contains nine invited and peer-reviewed articles which are reviews or new research related to this topic from investigators addressing children's narrative memory, brain systems associated with memories for stress and trauma, characteristics of memories for traumatic events in the general population and in clinical samples, and factors influencing recall of childhood sexual abuse. Several of the articles deal with recovered memories for childhood abuse. The issue will be available for purchase after November 15, 1995. If you are interested in purchasing a single copy for $20, please contact the International Society for Traumatic Stress Studies at 60 Revere Drive, Suite 500, Northbrook, IL, USA 60062; fax: 708/480-9282; e-mail: istss@ripco.com. For multiple copies, contact Plenum via J. S. Canner & Co., 10 Charles Street, Needham Heights, MA, USA 02194; fax: 617/449-1767.

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